Group 3 Patients
Antivirals or Neutralising Monoclonal Antibodies (nMABs) for *Non-Hospitalised patients* with COVID-19
Guidance for use in GGC

Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2. Neutralising monoclonal antibodies (nMAB) bind to specific sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into cells and therefore inhibiting its replication.

Evidence suggests that nMABs and oral antivirals significantly improve clinical outcomes in non-hospitalised patients with COVID-19 who are at high risk of progression to severe disease and/or death. Key findings are as follows:

- Paxlovid™ (nirmatrelvir plus ritonavir)- administered orally as dual antiviral treatment in the EPIC HR trial resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 days of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19. (Hammond et al, 2022). The WHO has made a strong recommendation for the use of nirmatrelvir-ritonavir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).
- Final results from the Phase 3 MOVe-OUT trial show that the oral antiviral molnupiravir resulted in a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29 (6.8% in the molnupiravir group vs 9.7% in the placebo group, p=0.0218) (Bernal et al, 2021). The WHO has made a conditional recommendation for molnupiravir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).
- Sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death at day 29 by 85% in the interim analysis of the COMET-ICE trial (Gupta et al, 2021a). Final analysis of this trial shows a relative risk reduction of 79% (Gupta et al, 2021b). This study was done in pre-Omicron COVID-19 variants. There is evidence of reduced in-vitro neutralisation in the Omicron variants and in September 2022, the WHO made a strong recommendation against the use of sotrovimab in non-hospitalised patients (WHO, September 2022).

The above products have a conditional marketing authorisations for use in the treatment of COVID-19 in the UK as follows.

- Paxlovid™ for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.
- Molnupiravir for use in the treatment of mild to moderate COVID-19 in adults (aged 18 years and over) with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness.
- Sotrovimab (Xevudy™) for the treatment of symptomatic adults, and adolescents (aged 12 years and over and weighing at least 40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. **Exceptionally, sotrovimab may be considered where the above treatments are deemed unsuitable and its use is supported following MDT assessment. In general, within NHS GGC sotrovimab treatment will be reserved for renal dialysis patients only, to be used at the discretion of the clinicians caring for this cohort of patients.**

Remdesivir is also a 2nd line treatment option for treating non-hospitalised patients with COVID-19 with risk factors for disease progression. A three-day intravenous course of remdesivir administered within 7 days of COVID-19 symptom resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021). The WHO has made a conditional recommendation for

remdesivir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022). **For logistical reasons remdesivir is not a treatment of choice within NHS GGC for out-patient administration. It may be considered for pregnant patients (as first-line treatment) and complex individual cases and clinical areas that are able to deliver the three day treatment.**

General Eligibility Criteria

Patients should meet all of the eligibility criteria and none of the exclusion criteria.

Non-hospitalised patients with onset of COVID-19 are eligible to be considered for the treatments above if:

- SARS-CoV-2 infection is confirmed by either:
  - Polymerase chain reaction (PCR) testing OR
  - Lateral flow test (registered via gov.uk)

  AND
- Symptomatic with COVID-19 and showing no signs of clinical recovery.
  - The following are considered symptoms of COVID-19: feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhoea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum or phlegm, runny nose.

  AND
- The patient is a member of a 'highest' risk group (as defined in Appendix 1)

Available treatment options for eligible patients are:

- **First-line**: Paxlovid™ (nirmatrelvir plus ritonavir) (antiviral) or Remdesivir (antiviral) for pregnant patients only.
- **Second-line**: Molnupiravir (antiviral).

Please note:

- **there is no clinical data to support the above therapies for patients who test positive but are asymptomatic.**
- **Combination treatment with an nMAB and an antiviral is NOT routinely recommended.**
- **Retreatment of recurrent or prolonged infections in an individual patient should be discussed with one of the ID Consultants in normal working hours. Patients who have previously received treatment with an antiviral or nMAB, and who meet the eligibility criteria within this policy, may receive treatment under this policy for a subsequent infective episode, if clinically appropriate.**
- **Paxlovid has significant drug interactions – the interaction checker must be used before prescribing this medication.**

Children aged under 18 should be referred to national paediatric COVID MDT where assessment will be used to determine clinical capacity to benefit from the treatment. Remdesivir may be considered for children of all ages that are 40kg and above, for complex individual cases and clinical areas that are able to deliver the three day treatment – please contact Paediatric ID Consultants to discuss.

General Exclusion Criteria

Patients would not be eligible for treatment if any of the following apply:

- Requirement for hospitalisation for COVID-19
- Known hypersensitivity reaction to the active substances or to any of the excipients of medications as listed in their respective Summary of Product Characteristics (SmPC).
- New or additional oxygen requirements.

Where patients are ineligible for treatment under this policy, recruitment to the PANORAMIC trial, which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported. Information is at: https://www.nhsinform.scot/illnesses-and-conditions/infections-and-poisoning/coronavirus-covid-19/coronavirus-covid-19-treatments

Paxlovid™ (nirmatrelvir plus ritonavir) Eligibility Criteria

If the general criteria above are met, patients may be considered for treatment with Paxlovid™ if:

- Treatment is commenced within 7 days of symptom onset*
  AND
- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease (eGFR <30ml/min), but note off-label dosing guidance for CKD 4-5 below.
  AND
- Paxlovid™ treatment has been deemed safe following guidance from the appropriate specialty team(s) – see Appendix 2 for NHS GGC Patient Pathway and prescribing Guide. The accompanying National Clinical Guide for treatment with antivirals and nMABs is available at https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103218

Paxlovid™ Additional Exclusion Criteria

- Children aged less than 18 years
- Pregnancy or breastfeeding
- The patient is taking any of the medications listed in Appendix 2. Please contact pharmacy teams if further advice on potential interactions are required.

Paxlovid™ Cautions

Paxlovid™ is not licensed for the treatment of patients with advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease who are not hospitalised. However, off-label, adjusted dosing can be used in stage4-5 chronic kidney disease patient group and also in dialysis patients after appropriate evaluation and discussion of risks/benefits with the patient – please see dosing section below.

Dose modification in stage 3 chronic kidney disease (eGFR 30-59ml/min) is recommended as per the SmPC – please see dosing section below.

Please refer to the SmPC for Paxlovid™for detail on special warnings and precautions for use.

Paxlovid™ has a risk of serious adverse reactions due to interactions with other medicinal products (see Appendix 2 and www.covid19-druginteractions.org/checker for prescribing guidance).

Initiation of Paxlovid™, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid™, may increase plasma concentrations of medicinal products metabolised by CYP3A. Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid™, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of Paxlovid™.
- Loss of therapeutic effect of Paxlovid™ and possible development of viral resistance.

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering nirmatrelvir/ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Patients should be advised of the possible gastro-intestinal side-effects of treatment with nirmatrelvir/ritonavir (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If nirmatrelvir/ritonavir treatment cannot be tolerated, an alternative treatment can be considered within the options and criteria of this policy. Combination treatment should not be provided unless in the context of a clinical trial.

Remdesivir Eligibility Criteria for First Line use in Pregnant Patients

- Treatment is commenced within 7 days of symptom onset.

Remdesivir Additional Exclusion Criteria

- Estimated glomerular filtration rate (eGFR) <30 mL/min (except in patients with end-stage renal disease on haemodialysis)
- Alanine transaminase (ALT) ≥ 5 times the upper limit of normal.
- Known hypersensitivity reaction to the active substances or to any of the excipients of remdesivir as listed in the Summary of Product Characteristics for Great Britain and Northern Ireland.

Remdesivir Cautions

- • ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- • ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated
Please refer to the SmPC for Remdesivir for a fuller list of side effects and precautions for use.

Molnupiravir Eligibility Criteria

If the initial criteria above are met, patients should only be considered for treatment with molnupiravir if:

- Treatment with Paxlovid™ is contraindicated or not possible
  AND
- Treatment is commenced within 7 days of symptom onset*

Molnupiravir Additional Exclusion Criteria

The following additional exclusion criteria applies if considering treatment with molnupiravir:

- Children aged less than 18 years
- Pregnancy

Molnupiravir Cautions

Please refer to the SmPC for molnupiravir for special warnings and precautions for use.

The most common adverse reactions (≥1% of subjects) reported during treatment and during 14 days after the last dose of molnupiravir were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

Sotrovimab Eligibility Criteria

If the general criteria above are met, patients may be considered for treatment with sotrovimab **by exception** if:

- the above antiviral medicines are contraindicated or not deemed suitable
  AND
- Endorsement of treatment has been sought and approved by a relevant MDT.
  Note: renal dialysis patients may receive treatment with sotrovimab without MDT approval.
  AND
- Treatment is commenced within 7 days of symptom onset*

Sotrovimab Additional Exclusion Criteria

- Children aged under 12 years
- Adolescents (aged 12-17) weighing 40kg and under

Patients who have received an nMAB within a post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) trial (such as the PROTECT-V trial) who meet the eligibility criteria of this policy can still receive treatment with sotrovimab, if this is deemed the most appropriate treatment option

Sotrovimab Cautions

Please refer to the SmPC for sotrovimab for special warnings and precautions for use.

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. These reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing.

If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated.

If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered.

The nMAB therapy is not intended to be used as a substitute for vaccination against COVID-19.

***Please note treatment commencement for all of the above medicines beyond 5 days from symptom onset is off-label.**

Paxlovid™ Dosing & Administration

The recommended dose of Paxlovid™ (nirmatrelvir plus ritonavir) is

- 300mg (two 150mg tablets) nirmatrelvir
  with
- 100mg (one 100mg tablet) ritonavir taken together **orally twice daily for 5 days only**. Treatment must not be extended beyond 5 days.
-

Dose Reduction Stage 3 Chronic Kidney Disease (eGFR 30-59ml/min)

The recommended dose of Paxlovid™ (nirmatrelvir plus ritonavir) is

- 150mg (one 150mg tablet) nirmatrelvir
  with
- 100mg (one 100mg tablet) ritonavir taken together **orally twice daily for 5 days only**. Treatment must not be extended beyond 5 days.

The remaining tablets of nirmatrelvir should be disposed of in accordance with local requirements.

Off-Label Dose Reduction for Stage 4-5 Chronic Kidney Disease and Dialysis

Renal Function	Licensed Dose	Proposed Dose
eGFR < 30 ml/min	Do not use	300mg nirmatrelvir + 100mg ritonavir once daily D1 Followed by 150mg nirmatrelvir + 100mg ritonavir once daily D2-5
Dialysis	Do not use	**Patients ≥ 40kg – to be given after dialysis** 300mg nirmatrelvir + 100mg ritonavir once daily D1 Followed by 150mg nirmatrelvir + 100mg ritonavir once daily D2-5 **Patients < 40kg – to be given after dialysis** 150mg nirmatrelvir + 100mg ritonavir once daily D1, D3, D5 ie every 48h for THREE doses only,

(Reproduced from http://www.covid19-druginteractions.org/prescribing_resources/paxlovid-renal-dosing)

Paxlovid™ should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms (*see above re day 6-7 post onset of symptoms). Clinicians should assure themselves that patients are able to swallow the oral tablets. Ideally, the tablets must not be crushed or dissolved and can only be taken orally. There is information about off-label use by crushing the tablets here: http://www.covid19-druginteractions.org/prescribing_resources/paxlovid-crushing-tablets. They may not be suitable in patients where the enteral route is compromised.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with Paxlovid™, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

To reduce the possibility of emerging resistance, patients should be advised to complete the whole course of treatment even if their symptoms improve and/or they feel better.

Remdesivir Supply, Dosing, Duration and Administration

Supply

Supplies can be obtained from departments of pharmacy during opening hours via an indent for a named patient supply. Please do not call an on-call pharmacist out for supply. Some supplies of loading doses are available in emergency drug cupboards.

Dose

The recommended dosage for Group 3 patients is a single loading dose of 200mg remdesivir intravenously on day 1, followed by a once daily maintenance dose of 100mg remdesivir for the remainder of the treatment course, which should not exceed 3 days.

Duration of treatment

Outpatient treatment duration is 3 days. Patients subsequently admitted for symptoms of COVID-19 (and meeting the eligibility criteria) should be considered for course of up to 5 days upon admission as per Group 1 patient guidelines.

Administration

200mg of remdesivir (day 1 loading dose) and 100mg of remdesivir (days 2-3 maintenance doses) should be diluted in either a 250ml or 100ml pre-filled bag of 0.9% sodium chloride solution and infused over a minimum of 30 minutes.

Side effects and monitoring

Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Remdesivir should be discontinued in patients who develop any of the following:

- ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)

Molnupiravir Dosing & Administration

The recommended dose of molnupiravir is **800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days only**. Treatment must not be extended beyond 5 days.

Clinicians should assure themselves that patients are able to swallow the oral capsules. The capsules are quite large but must not be crushed, opened or dissolved and can only be taken orally. They may not be suitable in patients where the enteral route is compromised.

Molnupiravir should be commenced as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset (*see above re day 6-7 post onset of symptoms).

To reduce the possibility of emerging resistance, patients should be advised to complete the whole course of treatment even if their symptoms improve and/or they feel better. If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with molnupiravir, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

Sotrovimab Dosing & Administration

The recommended **dose of sotrovimab is a single 500 mg intravenous infusion** administered following dilution.

Sotrovimab must be diluted in a single 100mL bag of 0.9% sodium chloride or glucose 5% (do not require to remove an equivalent volume of saline) - total volume 108mL and given over a minimum of 30 minutes via 0.2 micron inline filter.

The SmPC refers to allowing the vials to reach room temperature before use. This is for reasons of patient comfort during administration. If the diluent bag used is at room temperature, there is no need to allow the vial to warm first.

- **Sotrovimab must not be infused concomitantly in the same intravenous line with other medication. Repeat doses should not be administered**.
- Hypersensitivity reactions, including anaphylaxis, have been reported with administration of sotrovimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.
- Infusion-related reactions (IRRs) have been observed with IV administration of sotrovimab. IRRs observed in clinical studies were mostly mild to moderate in severity. The commonly reported signs and symptoms for these reactions are nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Pregnancy and Women of Childbearing Potential

Clinicians should refer to the SmPCs for the relevant products for further information on use in pregnancy and women of childbearing potential. **Paxlovid™ and molnupiravir require particular attention to the detail**

All healthcare professionals are asked to ensure that any patients who receive a COVID-19 antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 so that they can be followed up. For more information go to http://www.uktis.org/.

There are no human data on the use of **Paxlovid™** during pregnancy to inform the drug-associated risk of adverse developmental outcomes - women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid™. **Paxlovid™ is not recommended during pregnancy and in women of childbearing potential not using effective contraception**.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid™.

There limited amount of data from the use of **remdesivir** in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see below, SmPC and RCOG website for further information).

Remdesivir SmPC (Version 19/07/2023):

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of remdesivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures of the major metabolite of remdesivir that were around

human therapeutic exposures. Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it.

RCOG Guidance (updated 15/12/2022) https://app.magicapp.org/#/guideline/LqgJ3E

- Remdesivir, an antiviral, may be considered in pregnant women with COVID-19 in community and hospital settings.
- Clinicians should be aware that the foetal risk profile of remdesivir is largely unknown. See SmPC for further information.

There are no data from the use of **sotrovimab** in pregnant women. The SmPC for sotrovimab states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus. Prescribers should discuss contraception post treatment as appropriate, taking into account the ½ life of sotrovimab is ~49 days.

There are no data from the use of **molnupiravir** in pregnant women. Studies in animals have shown reproductive toxicity. **Molnupiravir is not recommended during pregnancy**. Individuals of childbearing potential must use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir.

Fertility

There are no human data on the effect of **Paxlovid™** on fertility. No human data on the effect of **nirmatrelvir** on fertility are available. Nirmatrelvir produced no effects on fertility in rats. There are no human data on the effect of **ritonavir** on fertility. Ritonavir produced no effects on fertility in rats.

No human data on the effect of **remdesivir** on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see SmPC). The relevance for humans is unknown.

There are no data on the effects of **sotrovimab** on human male or female fertility. Effects on male and female fertility have not been evaluated in animal studies.

There were no effects on female or male fertility in rats at exposures to the **molnupiravir** active metabolite which were approximately 2 and 6 times the exposure in humans at the recommended human dose.

Breast-feeding

It is unknown whether **nirmatrelvir** is excreted in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of **ritonavir** on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Paxlovid™ and for 7 days after the last dose of Paxlovid™.

It is unknown whether **remdesivir** is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remedesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

There are no data on the excretion of **sotrovimab** in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known. Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Maternal IgG is known to be present in human milk.

It is unknown whether **molnupiravir** or any of the components of molnupiravir are present in human milk, affect human milk production, or have effect on the breastfed infant. Based on the potential for adverse reactions on the infant from molnupiravir, breast-feeding is not recommended during treatment and for 4 days after the last dose of molnupiravir

Co-Administration

Should patients in this group have a subsequent hospital admission, co-administration with corticosteroids, remdesivir and IL6-inhibitors is permitted with **sotrovimab** and **molnupiravir** and no drug-drug interactions are expected. **All potential interactions with Paxlovid™ must be assessed and mitigated prior to initiating treatment.**
For further information please visit the University of Liverpool COVID-19 Drug Interactions website: (https://www.covid19-druginteractions.org/checker).

Sotrovimab should not be regarded as an alternative to corticosteroids.

Monitoring, tracking and follow up

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly mention that an antiviral or nMAB for treatment of COVID-19 has been given and the date of administration.

There is an urgent need to generate more evidence and greater understanding around the use of antivirals and nMABs in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB treatment; the impact of nMAB treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB use, such as generation of new mutations.

Treating clinicians are asked to ensure that all PCR tests undertaken as an inpatient and/or in the community where any patient who is receiving ongoing PCR testing as part of secondary care (for example, through an outpatient clinic) should do this through the hospital laboratory (WoSSVC) where these samples will be sequenced if positive.

Monitoring of longer-term progress is strongly recommended via recruitment of patients receiving COVID therapies to the ISARIC-CCP study

Safety reporting

It is vital that any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) are reported directly to the

MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk

COVID-19 Vaccines

The Green Book states

"Monoclonal antibodies to COVID-19 have recently been licensed for the treatment and prophylaxis of COVID-19 infection. Primate data suggests that administration of the AstraZeneca combination monoclonal antibody product did not interfere with the subsequent response to active vaccination. Based on this limited evidence, therefore, no specific interval is required between receipt of these products and COVID-19 vaccination, or vice versa. As the use of these products is likely to be prioritised to those who are less able to respond to vaccination, for example immunosuppressed individuals, additional doses of vaccine may be required as outlined above"

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040677/Greenbook-chapter-14a-14Dec21.pdf

Appendix 1 Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs and Antivirals

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC). Please see full independent advisory group report at: https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report-march-2023

Box 1 Risk factors for progression to severe COVID-19 in adults

Risk factors for progression to severe COVID-19 in adults defined by the independent advisory group commissioned by the Department of Health and Social Care (June 2023)

Down's syndrome and other genetic disorders

All individuals with Down's syndrome or other chromosomal disorders known to affect immune competence

Solid cancer

- metastatic or locally advanced inoperable cancer
- lung cancer (at any stage)
- people receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy within 12 months
- people who have had cancer resected within 3 months and who received no adjuvant chemotherapy or radiotherapy
- people who have had cancer resected within 3 to 12 months and receiving no adjuvant chemotherapy or radiotherapy are expected to be at less risk (and thus less priority) but still at increased risk compared with the non-cancer populations

Haematological diseases and recipients of haematological stem cell transplant (HSCT)

- allogeneic HSCT recipients in the last 12 months or active graft versus host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases)
- autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases)
- individuals with haematological malignancies who have received CAR-T cell therapy in the last 24 months, or until the lymphocyte count is within the normal range
- individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months, or radiotherapy in the last 12 months
- all people who do not fit the criteria above, and are diagnosed with:
  - myeloma (excluding monoclonal gammopathy of undetermined significance [MGUS])
  - AL amyloidosis
  - chronic B-cell lymphoproliferative disorders (chronic lymphocytic leukaemia, follicular lymphoma)
  - myelodysplastic syndrome (MDS)
  - chronic myelomonocytic leukaemia (CMML)
  - myelofibrosis
  - any mature T-cell malignancy
- all people with sickle cell disease
- people with thalassaemia or rare inherited anaemia with any of the following:
  - severe cardiac iron overload (T2 * less than 10 ms)
  - severe to moderate iron overload (T2 * greater than or equal to 10 ms) plus an additional comorbidity of concern (for example, diabetes, chronic liver disease or severe hepatic iron load on MRI)
- individuals with non-malignant haematological disorders (for example, aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (for example, anti-CD20, anti-thymocyte globulin [ATG] and alemtuzumab) within the last 12 months

Renal disease

- renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who have:
  - received B-cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], ATG)
  - an additional substantial risk factor which would in isolation make them eligible for monoclonals or oral antivirals
- non-transplant renal patients who have received a comparable level of immunosuppression
- patients with chronic kidney disease (CKD) stage 4 or 5 (an estimated glomerular filtration rate [eGFR] less than 30 ml per min per 1.73 m^2) without immunosuppression

Liver diseases

- people with cirrhosis Child-Pugh (CP) class A, B and C, whether receiving immune suppressive therapy or not. Those with decompensated liver disease (CP B and C) are at greatest risk
- people with a liver transplant
- people with liver disease on immune suppressive therapy (including people with and without cirrhosis)

Solid organ transplant recipients

Solid organ transplant recipients not in any of the above categories

Immune-mediated inflammatory disorders (diseases in which autoimmune or autoinflammation-based pathways are implicated in disease, for example, inflammatory arthritis, connective tissue diseases, inflammatory skin diseases, inflammatory gastrointestinal disease)

- people who have received a B-cell depleting therapy (anti-CD20 drug, for example, rituximab, ocrelizumab, ofatumab, obinutuzumab) in the last 12 months
- people who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR or relevant COVID test
- people who are on corticosteroids (equivalent to or greater than 10 mg per day of prednisolone) for at least the 28 days prior to positive PCR
- people who are on biologics or small molecule JAK inhibitors
- people who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine, mercaptopurine, or similar agents (for major organ involvement such as kidney, gastro-intestinal tract, liver, lung, brain), methotrexate (for interstitial lung disease or asthma only) and/or ciclosporin. No minimum dose threshold is suggested
- people who are on current treatment (or within the last 6 months) with S1P modulators (fingolimod, ponesimod or siponimod), or alemtuzumab or cladribine within the last 12 months
- people who exhibit at least one of: (a) uncontrolled or clinically active disease (that is, required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) other high risk comorbidities (for example, body mass index [BMI] greater than 30, diabetes mellitus, hypertension, major organ involvement such as significant kidney, liver, nervous system or lung inflammation or significantly impaired renal, liver, nervous system and/or lung function)

Respiratory

- asthma in people on oral corticosteroids (defined above). Any asthma patient taking immunosuppressants for their asthma including but not exclusively methotrexate, ciclosporin
- COPD on long term home non-invasive ventilation (NIV). Patients on long term oxygen therapy. People with moderate or severe disease (FEV1 less than or equal to 50% predicted) who have required 4 or more courses of prednisolone 30 mg for 5 days or greater in last 12 months
- interstitial lung disease (ILD) – all patients with idiopathic pulmonary fibrosis
- sub-types of ILD, for example, connective tissue disease related, sarcoidosis, hypersensitivity pneumonitis, NSIP (non-specific interstitial pneumonia) who have received a B-cell depleting therapy in last 12 months, or IV or oral cyclophosphamide in the 6 months prior to testing positive for COVID-19. Any ILD patient on current treatment with corticosteroids, mycophenolate mofetil, azathioprine, tacrolimus, cyclosporin or methotrexate. No minimum dose criteria

- any people with any type of ILD who may not be on treatment due to intolerance but has severe disease with an FVC predicted less than 60%
- NIV and tracheostomy ventilated – all patients requiring this type of support regardless of the underlying disorder (which might include COPD, obesity hypoventilation syndrome, scoliosis, bronchiectasis, neurodisability and genetic muscular diseases [refer to neurology section]).
- lung cancer patients, refer to 'Solid cancer' section above
- lung transplant patients (refer to solid organ transplant section)
- pulmonary hypertension (PH): groups 1 and 4 from PH classification

Immune deficiencies

- common variable immunodeficiency (CVID)
- undefined primary antibody deficiency on immunoglobulin (or eligible for Ig)
- hyper-IgM syndromes
- Good's syndrome (thymoma plus B-cell deficiency)
- severe combined immunodeficiency (SCID)
- autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- primary immunodeficiency associated with impaired type 1 interferon signalling
- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)
- any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy

HIV/AIDS

- people with high levels of immune suppression, have uncontrolled or untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis
- people on treatment for HIV with CD4 less than 350 cells per mm3 and stable on HIV treatment or CD4 greater than 350 cells per mm3 and additional risk factors (for example, age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, alcoholic dependency)

Neurological disorders

- Conditions associated with neuromuscular respiratory failure requiring chronic ventilatory support:
  - motor neurone disease
  - Duchenne muscular dystrophy
- Conditions that require use of specific immunotherapies:
  - multiple sclerosis (MS)
  - myasthenia gravis (MG)
  - other immune-mediated disorders
- Dementia, neurodegenerative and neuroimmune disorders when associated with severe frailty (for example, levels 7 or 8 on Clinical Frailty Scale, as part of a personalised care plan):
  - Alzheimer's disease, vascular disease, Lewy body disease, or frontotemporal atrophy
  - Parkinson's disease
  - Huntington's disease
  - progressive supranuclear palsy and multiple system atrophy
  - motor neurone disease
  - multiple sclerosis and other immune-mediated neurological disorders

Box 2 Risk factors for progression to severe COVID-19 in young people aged 12 to 17 years

Pathway for PCR positive symptomatic cases aged older than 12 and younger than 18 years, greater than 40 kg weight, and clinical concern: defined by the independent advisory group commissioned by the Department of Health and Social Care (March 2023)

Non-hospitalised individuals in the older than 12 and younger than 18 years age range considered at high risk from COVID-19 and to be prioritised for consideration of treatment with neutralising monoclonal antibodies when symptomatic and SARS-CoV-2 PCR positive. Concerned clinicians should refer for regional multidisciplinary team (MDT) case discussion through local established pathways, who will confirm eligibility and consider risk benefit and whether to proceed with offer of treatment.

Children and young people (CYP) at substantial risk

Complex life-limiting neurodisability with recurrent respiratory infections or compromise.

CYP at significant risk if 2 or more of these risk factors are present

Primary immunodeficiency:

- common variable immunodeficiency (CVID)
- primary antibody deficiency on immunoglobulin (or eligible for immunoglobulin replacement)
- hyper-IgM syndromes
- Good's syndrome (thymoma plus B-cell deficiency)
- severe combined immunodeficiency (SCID)
- autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- primary immunodeficiency associated with impaired type 1 interferon signalling
- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)

Secondary immunodeficiency:

- HIV CD4 count less than 200 cells per mm3
- solid organ transplant
- haematological stem cell transplant (HSCT) within 12 months, or with graft versus host disease (GVHD)
- CAR-T cell therapy in last 24 months
- induction chemotherapy for acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphoma, chemotherapy for acute myeloid leukaemia (AML), relapsed and/or refractory leukaemia or lymphoma

Immunosuppressive treatment:

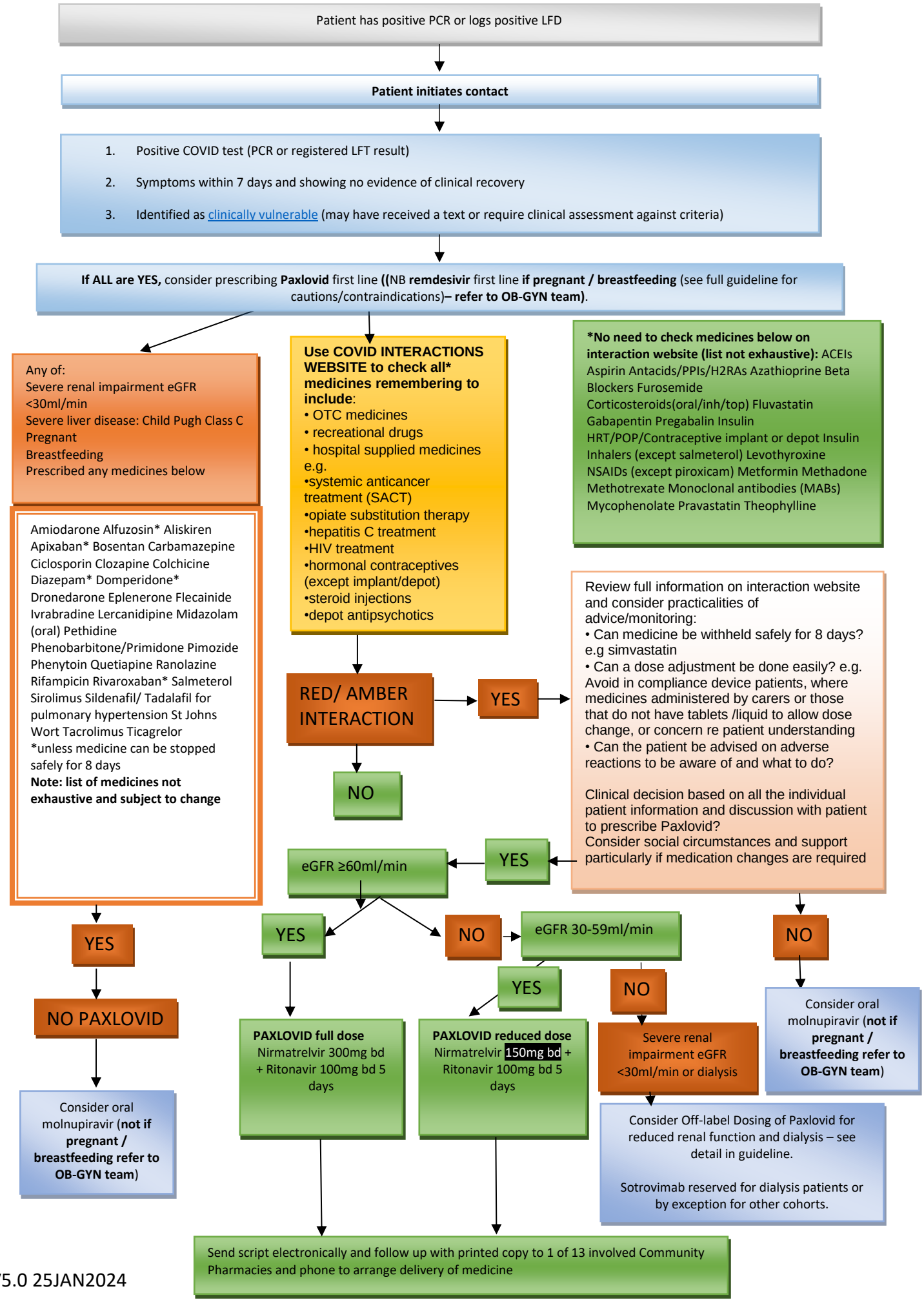
- chemotherapy within the last 3 months
- cyclophosphamide within the last 3 months
- corticosteroids greater than 2 mg per kg per day for 28 days in last 4 weeks
- B-cell depleting treatment in the last 12 months

Other conditions:

- high body mass index (BMI; greater than 95th centile)
- severe respiratory disease (for example, cystic fibrosis or bronchiectasis with FEV1 less than 60%)
- tracheostomy or long-term ventilation
- severe asthma (paediatric intensive care unit [PICU] admission in 12 months)
- neurodisability and/or neurodevelopmental disorders
- severe cardiac disease
- severe chronic kidney disease
- severe liver disease
- sickle cell disease or other severe haemoglobinopathy
- trisomy 21
- complex or chromosomal genetic or metabolic conditions associated with significant comorbidity
- multiple congenital anomalies associated with significant comorbidity

- bronchopulmonary dysplasia – decisions should be made taking into account degree of prematurity at birth and chronological age
- infants less than 1 year with congenital heart disease (CHD):
    - cyanotic CHD
    - haemodynamically significant acyanotic CHD and history of prematurity
    - those due for corrective surgery, to avoid complications or delay due to SARS-CoV-2 infection

Appendix 2 Patient Pathway in NHS GGC and Prescribing Guidance



Document History

Version	Date	Description
1.0	22/12/2021	Approval of First Release after MHRA CAS Alert 16/12/2021
1.1	19/01/2022	Detail added re accessing treatment
2.0	16/02/2022	Review after MHRA CAS Alert 27/01/2022
3.0	19/09/2022	Review after MHRA CAS Alert 30/05/2022
4.0	29/12/2022	Review after MHRA CAS Alert 28/11/2022
5.0	09/01/2024	Routine review; update high risk cohorts as per NICE TA878 22/06/2023; document history added. Minor changes to text. Add detail for remdesivir use in pregnancy, fertility & breast feeding sections.

COVID-19
CLINICAL GUIDELINE

Note: This guideline has been fast-tracked for approval for use within NHSGGC

Covid-19 Group 3 Patients Antivirals or Neutralising Monoclonal Antibodies (nMABs) for Non-Hospitalised patients with COVID-19

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

Version Number:	6
Does this version include changes to clinical advice:	Yes
Date Approved:	31st January 2024
Approval Group:	Covid 19 Tactical Group (Acute)

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.